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American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

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Vol. 125 MAY 1953 No. 5

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EDITORIAL

THE SHORTAGE OF PHARMACISTS

SINCE 1941, the demand for licensed pharmacists has exceeded the available supply. This fact is deplored by some in our ranks while to others it is a source of great satisfaction. The underlying causes for this development are quite complex but we shall try as best we can to discuss them.

The war years were responsible for at least two of the causes of the present shortage: a drastic reduction in the college enrollment of pharmacy students and an increased demand for manpower in the armed services. This, over several years, resulted in an accumulated deficit. The later war years and the post-war period were accompanied by a rapidly expanding economy and a population growth which caused an even greater demand for trained personnel: physicians, pharmacists and nurses as well as technical specialists in all fields. Some fields, notably engineering, which were allegedly overcrowded just a few years ago now report an accumulated shortage running into many thousands. So severe is this shortage that one company has agreed to pay a college or university a three thousand dollar premium for each engineering graduate joining the company and remaining for one year. The need for physicians, while denied in some quarters, is a matter known only too well in certain areas of the country. These facts are cited so that one will not make the mistake of believing that it is in the field of pharmacy alone that the demand for trained personnel exceeds the supply.

One very important development explaining the demand for pharmacists is the expansion of opportunities for pharmacists in other than retail establishments. Much of this is directly attributable to the improvement in pharmaceutical education which has taken place, both by reason of the introduction of a four year course in the thirties and the extensive up-grading which has taken place in pharmaceutical education, particularly over the past few years. Government and industry have learned by experience that it pays to place trained pharmacists in many positions which were once filled either by other scientists or untrained personnel.

Not only has the population of the United States grown rapidly in the last decade, but there has been an unprecedented rise in our standard of living. The public is well informed today on the availability of our "wonder drugs" and it demands their use not just for the wealthy, privileged few but for every person who needs such therapy. Never before in history were the poor as well taken care of in their health needs as today. The American drug industry is fully twice its pre-war size in both capital investment and production and, as a result, this means a greatly expanded need for personnel—in production, research, distribution and sales.

To make the situation still more acute the work week of the pharmacist has dropped steadily. Only a few years ago the pharmacist almost invariably worked sixty hours and upwards a week. Today forty-eight to forty-four hours is customary and many pharmacists work only a forty hour week. Obviously it takes more pharmacists to perform necessary services working fewer hours.

There is, however, nothing in the present situation to cause alarm or to encourage emergency measures. A shortage of trained personnel in any field is a wholesome thing, for it improves the professional, economic, and social position of such persons who are in demand. Surely no one would want to see the return of those days in the twenties when pharmacists were grossly exploited; then there were two or three begging for each available job. In no field other than pharmacy are the practitioners bewailing the shortage of personnel. They are wise enough to recognize the advantages which such a situation bestows on those engaged in such work.

In pharmacy, however, as might be expected, things are different. Some prospective employers who seek cheap help often set up a hue and cry concerning the dire consequences which will result to pharmacy and the nation unless the supply of pharmacists is such that men are happy to work a sixty hour week for a fifty dollar salary. These same employers will tell you that they can't afford to pay the prevailing rate, and possibly they can't. If such is the case then we might suggest that it would be wise for them to close their establishments and work as employee pharmacists for someone else. We suspect that there are many marginal pharmacies which by closing would improve our professional status and not in any sense detract from the public welfare.

Pharmacists who respect their profession should guard carefully against any attempt to lower the required qualifications for admis-

sion to practice, whether it be on the college or state board level. Already we have heard rumors that some such suggestions have been made. Pharmacists must not be deceived into believing that lowered standards help those in practice. Such action may for a short time provide cheap help but in the final analysis it makes for cut-throat competition and a disregard of professional ethics and standards. Is there any pharmacist who longs for the good old twenties?

Pharmacists should also reject the suggestion, from whatever source it comes, that a shortage of pharmacists will cause a serious shortage of pharmaceutical service and be detrimental to public health. This is specious in view of the claim made by these same "experts" that pharmacists must merchandise clocks, cutlery and china in order to survive. It would be a great day for pharmacy if most of every pharmacist's time were taken up giving pharmaceutical service!

Yes, there is a shortage of pharmacists and this is healthful and wholesome for the profession. We must resist the efforts of those who would have it otherwise.

L. F. Tice

STUDIES ON PYTHIUM DEBARYANUM, Hesse FOR ANTIBACTERIAL ACTIVITY *

By Lewis Debes † and Henry M. Burlage ‡

Introduction

PYTHIUM DEBARYANUM, Hesse is described by Matthews (1) as follows: "Mycelium well developed in host tissues and when grown in cultures. Hyphae branched, usually about 5μ in diameter, often septate in old cultures. Sporangia few, spherical to oval, terminal, or intercalary. Conidia numerous, same size as the sporangia, germinating by a germ tube soon after being formed, while still attached to the hypha or after falling off and a long or short rest period. Oogonia smooth, terminal or intercalary, usually spherical, 15-25μ in diameter. Oospores smooth, not filling the oogonium, 10-18μ in diameter, germinating directly after a rest of several months. Antheridia 1-6 to an oogonium, diclinous, androgynous and hypogynal, when androgynous often arising at some distance from the oogonium."

It has been reported as a parasite or saprophyte and is especially destructive to young seedlings causing a disease known as "damping off." The plants which this species of Pythium affects include certain conifers, sugar beets, tobacco, tomatoes, potatoes, sugar cane, banana, pineapple, rice, egg plant, celery, barley, oats, maize, cabbage, cucumber, peas, sweet potato, and certain plants used as flowers. (1)

This fungus is not a fastidious one from the nutritional point of view but is extremely so for its temperature requirements. McLaughlin (2) found that a combination of high soil temperatures with low moisture resulted in a reduction in the percentage of Pythium isolates; therefore the fungus showed greater yields during the winter, fall, and spring than during the summer. The optimum range of temperature for maximum yield of Pythium mycelium is between 24°-27° C. However the amount of media used is related to the surface area of the flask, and consequently 150cc. of a synthetic medium (dextrose

* These studies were supported by funds granted to the Pharmaceutical Foundation of the College of Pharmacy of The University of Texas by Sharp and Dohme, Inc. of Philadelphia, Pa.

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75 Gm., $NaNaO_3$ 2 Gm., $MgSO_4$ 0.5 Gm., KH_2PO_4 1 Gm., yeast extract 4 Gm., peptone 6 Gm., water 1 L.) has been shown to be the necessary amount in obtaining the maximum growth of the fungus.

Experimental Work

Cultures of *Pythium debaryanum* were maintained on Waksman's agar at a pH of 6.2-6.6. An inoculum of the mycelium was transferred to each of twelve test tubes containing 10cc. of the synthetic medium and incubated at room temperature (24°-27° C.) for 3 days. After incubation, the mycelium was transferred to twelve one-liter flasks containing 150 cc. of similar medium and incubated 2 to 4 weeks. At the end of incubation, the mycelium was harvested by the use of a sterile Buchner funnel and filter paper (Whatman No. 1).

A number of organic solvents were used to extract the mycelium and each extract was tested for its antibacterial activity against the following organisms *: *Salmonella typhosa, Salmonella paratyphi A, Salmonella paratyphi B, Shigella dysenteriae, Neisseria catarrahalis, Escherichia coli, Proteus vulgaris, Bacillus subtilis, Pseudomonas aeruginosa,* and *Staphylococcus aureus.* The cup-assay method as described by Foster and Woodruff (3) was first used to determine if the extracts of *P. debaryanum* were antibacterial. Because of the slow diffusability of the crude extract through agar in this method, a cup was made directly in the agar by means of a cork borer (No. 3). Also used was the filter paper disc as was described by Vincent and Vincent (4).

Procedure used in testing antibacterial activity

With a sterile pipette an inoculum of 20 hour cultures of the test organisms was placed into melted nutrient agar. The seeded nutrient agar was poured into a sterile petri dish containing agar and rotated to obtain an even dispersion and was then permitted to solidify at room temperature. With the aid of a cork borer (No. 3) three holes were made into the seeded agar plate. Using a sterile pipette, enough of the water-soluble portion of the extract was placed into one of the holes, in the seeded agar. The second hole contained the "Wesson oil" soluble portion of the extract. As a control, normal saline solution

* We wish to thank Dr. O. B. Williams of the Department of Bacteriology of The University of Texas for furnishing these organisms.

was used. The plates so prepared were incubated for 24 hours and examined for zones of inhibition, the radii of which were measured in millimeters.

The sterile filter paper disc was placed on the surface of seeded agar and five drops of the test substance were added to the disc. (The disc can be immersed into the test solution for 30 seconds and then placed on the agar.) The seeded agar plates were incubated and zones of inhibition were measured as above.

Preparation of the Extracts

(A) Ether Extract of the Mycelium by Use of the Soxhlet Apparatus

The extraction was continued until solution was completed, the solvent was evaporated under vacuum and a lemon-yellow oil with a pungent odor was obtained (0.0804 Gm.) and this residue was treated with sufficient sterile distilled water to make a solution equivalent to 15.5 mg. of the extract per ml. The extract so prepared when tested by the Cup method was *negative* in its action upon the test organisms.

(B) Ether Extract Obtained by Percolation of the Mycelium

Since heat was employed in preparing the ether extract in (A) and showed negative results, an extract was prepared by percolation avoiding the use of heat. A lemon-yellow oil with a pungent odor (0.0614 Gm.) was obtained, and was treated with sufficient sterile distilled water to make a solution equivalent to 8.6 mg. of the extract per ml. This extract when tested by the Cup method gave *negative* results in its action on the test organisms.

(C) Chloroform Extract of the Mycelium

This extract was prepared by percolation and after evaporation of the solvent a light brownish-yellow oil with a pungent odor (0.0584 Gm.) was obtained, and was treated with sufficient sterile distilled water to make a solution equivalent to 7.3 mg. of the extract per ml., and when tested by the Cup method was negative in its action on the test organisms.

(D) Water Extract of the Lyophilized Mycelium

Ten grams of the mycelium were placed in a cold sterile mortar and 5 grams of alundum (90 mesh) were added and the mycelium

ground for 20 minutes, after which it was transferred to a cold sterile flask containing sterile distilled water. The flask and its contents were placed in a refrigerator overnight after which it was filtered by means of a sterile bacterial filter and the filtrate was lyophilized under reduced pressure. The residue (0.542 Gm.) was dissolved with sufficient sterile distilled water so that the solution was equivalent to 100 mg. per ml. It was then tested against the test organisms using the Cup method and was found to be negative.

(E) Ether Extract (Lyophilized) of the Mycelium

This extract was prepared by the same procedure in (D), as (0.090 Gm.) was treated with sufficient sterile distilled water so that it was equivalent to 45 mg. of the extract per ml. It was tested against the test organism by the Cup method and was found to be negative.

(F) Ether Extract (Lyophilized) of the Mycelium

The mycelium was placed in a cold sterile mortar and ground for 20 minutes with 5 grams of alundum (90 mesh) and this was transferred to a Waring blendor and was treated with 200 ml. of ether in 50 ml. portions. The ether-mycelium mixture was transferred to a cold sterile flask and placed in a refrigerator overnight, after which the mixture was filtered through a cold sterile bacterial filter and the filtrate was lyophilized under reduced pressure. The extract (0.425 Gm.) was treated with sufficient sterile distilled water so that a solution was equivalent to 100 mg. of the extract per ml. All tests were negative.

The extract treated with a sterile buffer soluton (pH = 7.0) and using the "hole" method gave *negative* results. Results by the disc method were also *negative*.

Effects of the Extracts of Pythium on Chick Embryos and Tumors of Tumor-bearing Eggs *

Extracts of Pythium mycelium were tested for their effects on the growth of embryos and tumors of tumor-bearing eggs. A total of 11 experiments involving 176 eggs bearing yolk sac implants of C3H mouse mammary carcinoma were completed. The results of these tests are outlined in the accompanying table (Table I).

* Tests were performed by Dr. Alfred Taylor and his co-workers in the Biochemical Institute, The University of Texas.

TABLE I

EFFECTS OF EXTRACTS OF PYTHIUM ON GROWTH OF CHICK EMBRYOS AND OF TUMORS OF TUMOR-BEARING EGGS

Suspending Medium Cottonseed Oil and H_2O (2:1) Membrane Injection 24 Hour Test Period

Extract Type	Dosage	No. Eggs	Age of Embryo at Time of Injection (Days)	Survival C = 100	Average Growth of Exp. Group for test period	
					Tumor	Embryo
cold H_2O	.07 cc	8	11	100	69	100
hot H_2O	.07 cc	8	11	100	88	123
Acetone	.07 cc	8	11	100	135	79
NaOH	.07 cc	8	11	95	55	100
HCl	.07 cc	8	11	81	144	118
cold H_2O unfiltered	.07 cc	8	11	100	87	100
Acetone	.2 mg	8	11	100	125	97
Alcohol	.2 mg	8	11	75	59	113
Alcohol lyophilized	.1 mg	8	11	100	92	111
Alcohol	.07 cc	8	12	100	86	109
Percolate lyophilized	.1 mg	8	12	100	150	116

Some of the extracts inhibited tumor growth while others accelerated the growth of both tumor and embryo. In no instance was the effect such as to warrant further study with these particular extracts, since, on the basis of experience, a particular compound or extract should inhibit tumor growth consistently more than 50% to merit additional research in this regard. However, further studies are planned to examine the growth-promoting substance which was apparent in six of these eleven tests.

Some antibiotic activity was exhibited by the water extract; this was equivalent to about one-tenth of the effect produced by penicillin, prolonging the life of chick embryos against injection of "pooled" bacteria.

Discussion

Several organic solvents were used in attempts to extract possible antibacterial substances from *Pythium debaryanum*, Hesse, and

negative results were obtained when the extracts were tested for antibacterial activity against ten test organisms.

Some extracts inhibited tumor growth in tumor-bearing eggs, while others showed an acceleration of growth of both tumor and embryo.

Pythium debaryanum does not produce any metabolic or degradation products in the liquid media.

Further investigations of the extracts of *Pythium debaryanum*, especially those lipid-like in character, are being planned.

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THE ANALEPTIC ACTIVITY OF SIX CONVULSANT BARBITURATES IN ACUTE BARBITURATE POISONING IN MICE *

By Charles A. Leonard ** and Joseph W. E. Harrisson **

MANY barbituric acid derivatives manifest convulsant action rather than hypnotic action and there are a number of reports on experiments with convulsant barbiturates suggesting their possible use in barbiturate poisoning (1, 2, 3, 4, 5). Some of these compounds have been included in this study in which a different method for determination of analeptic activity has been used.

The purpose of the study was to test convulsant barbituric acid derivatives as possible analeptics for use in acute barbiturate poisoning in mice and as antagonists to the hypnotic effect of the same drugs. Hexobarbital Sodium (Evipal Sodium (R) [1]) and Pentobarbital Sodium were employed as the experimental barbiturates. The method for determination of analeptic activity was based on that suggested by Goodwin and Marshall (6). This method has been employed in our laboratory for the past year in tests involving analeptic combinations.

It was hoped that the convulsant barbiturates might act as analeptics as well as antagonists to the hypnotic barbiturates due to structural analogy.

Preliminary Experiments

The minimum effective (convulsant) and maximum tolerated dose of each of the convulsant barbiturates were determined by intraperitoneal administration. This data is reported in Table I. Likewise the minimum hypnotic and LD_{50} dose of Pentobarbital Sodium and Hexobarbital Sodium were ascertained. In each instance this preliminary work was undertaken on the strain of mice to be employed later in the study.

* Supported by a research grant from Eli Lilly and Co., Indianapolis, Indiana.

** From the LaWall Memorial Laboratory of Biochemistry and Pharmacology.

1. Evipal Sodium(R) was generously supplied by Winthrop-Stearns, Inc., New York 18, N. Y.

TABLE I

COMPOUNDS TESTED, PREDOMINANT EFFECT, AND DOSAGES

Compound	Predominant Effect	Minimum Convulsive Dose	LD_0
Lilly 09757 5-(1, 3 Dimethyl Butyl) 5-Ethyl Barbituric Acid (Sod. Salt)	Convulsant	15 mg/Kg i.p.	25 mg/Kg i.p.
Lilly 14707 1-*n*-Butyl, 5-Ethyl, 5-Methyl Barbituric Acid (Sod. Salt)	Convulsant	350 mg/Kg i.p.	600 mg/Kg i.p.
Lilly 12412 5-(3, 3 Dimethyl Allyl) 5-Ethyl Barbituric Acid (Sod. Salt)	Convulsant	200 mg/Kg i.p.	300 mg/Kg i.p.
5-Butyl Barbituric Acid (Sod. Salt)	Convulsant	2 grams/Kg i.p.	5 grams/Kg i.p.
5-Ethyl, 5-Benzyl Barbituric Acid (Sod. Salt)	Convulsant	35 mg/Kg i.p.	50 mg/Kg i.p.
5, 5 Dibenzyl Barbituric Acid (Sod. Salt)	Convulsant	200 mg/Kg i.p.	375 mg/Kg i.p.

The minimum effective dose (convulsant) of the convulsant barbiturate was then employed in the experimental work against both the minimum hypnotic and LD_{50} dose of the Pentobarbital Sodium and Hexobarbital Sodium.

Experimental

Two-hundred-eighty male Swiss mice (CFW) in a weight range of 22 ± 2 grams were selected and divided into four groups of seventy animals. Each group was subdivided into seven groups of ten animals. One subgroup served as control and received the hypnotic barbiturate followed by normal saline solution after ten minutes of sleep. The remaining subgroups received the hypnotic barbiturate followed by one of the convulsant barbiturates after ten minutes of sleep. All administrations were made intraperitoneally. The minute respiratory rate was recorded prior to the second injection and at fifteen and thirty minutes thereafter. The time of awakening was recorded and any unusual reactions noted. The criteria for "awaking"

and "sleeping time," as described previously (7), were used in this study.

During the period of sleep, the animals were placed in an incubator having a glass-paneled door for ease of observation. The incubator was maintained at 28° C. with forced circulation of fresh air. Tests in our laboratory have shown this environment to be optimum for tests of this nature. The data are reported in Tables II and III.

Discussion

Examination of the data from all groups shows, with a few exceptions, that the convulsant barbiturates appear to be synergistic to the hypnotic barbiturates with respect to increase in sleeping time and depression of respiration.

The compound 5-(3,3 dimethyl allyl) 5-ethyl barbituric acid manifested the greatest antagonism to an LD_{50} dose of Pentobarbital Sodium with regard to survival, which may not be significant but it increased sleeping time after a hypnotic dose of Pentobarbital Sodium. The same compound has somewhat less effect against the LD_{50} dose of Hexobarbital Sodium. The sodium salts of 5-ethyl, 5-benzyl barbituric acid and 5,5-dibenzyl barbituric acid appear to be outstanding against the LD_{50} dose of Hexobarbital Sodium; on the other hand, the sleeping time after administration of the minimum sleeping dose of Hexobarbital Sodium was prolonged. Survival was definitely increased after an LD_{50} dose of Hexobarbital Sodium and a slight increase in respiratory rate was manifested.

Observations of the effects of these convulsant barbiturates which were noted during the preliminary determination of dosages and during the course of this study agree with those made by Velluz et al. (8). These workers investigated similar compounds individually but not as hypnotic barbiturate antagonists.

Summary

1. Six convulsant barbiturates have been tested as possible antagonists against the hypnotic and toxic effects of the barbiturates, Hexobarbital Sodium and Pentobarbital Sodium in mice.

2. Three compounds have manifested some degree of analeptic activity when tested in this manner.

TABLE II

OBSERVED DATA WITH BARBITURATES AT THE HYPNOTIC DOSE LEVEL

Group			Mean Sleeping Time		Mean Respiratory Rate		
First Injection	Second Injection After 10′ of Sleep	Survival	Hours	Minutes	0′	15′	30′
Sod. Pentobarb. 45 mg/Kg i.p.	Normal Saline Solution—Control	10/10	—	48	192	182	165
"	5-(1, 3 Dimethyl Butyl) 5-Ethyl Barbituric Acid (Sod. Salt) 15 mg/Kg i.p.	10/10	1	8	192	177	168
"	1-*n*-Butyl, 5-Ethyl, 5-Methyl Barbituric Acid (Sod. Salt) 350 mg/Kg i.p.	10/10	3	34	181	127	68
"	5-(3, 3 Dimethyl Allyl) 5-Ethyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	10/10	1	4	177	168	140
"	5-Butyl Barbituric Acid (Sod. Salt) 2 grams/Kg i.p.	10/10	1	25	169	137	146
"	5-Ethyl, 5-Benzyl Barbituric Acid (Sod. Salt) 35 mg/Kg i.p.	10/10	1	10	166	Too Fast To Count	
"	5, 5-Dibenzyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	10/10	1	28	171	159	157
Hexobarbital Sodium 75 mg/Kg i.p.	Normal Saline Solution—Control	10/10	—	27	192	196	216
"	5-(1, 3 Dimethyl Butyl) 5-Ethyl Barbituric Acid (Sod. Salt) 15 mg/Kg i.p.	10/10	—	25	188	177	—
"	1-*n*-Butyl, 5-Ethyl, 5-Methyl Barbituric Acid (Sod. Salt) 350 mg/Kg i.p.	10/10	1	25	172	157	145
"	5-(3, 3 Dimethyl Allyl) 5-Ethyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	10/10	—	26	165	184	—
"	5-Butyl Barbituric Acid (Sod. Salt) 2 grams/Kg i.p.	10/10	—	44	159	169	153
"	5-Ethyl, 5-Benzyl Barbituric Acid (Sod. Salt) 35 mg/Kg i.p.	10/10	2	2	174	170	157
"	5, 5-Dibenzyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	10/10	1	29	164	159	167

TABLE III

OBSERVED DATA WITH BARBITURATES AT THE LD_{50} DOSE LEVEL

Group			Mean * Sleeping Time		Mean ** Respiratory Rate		
First Injection	Second Injection After 10′ of Sleep	Survival	Hours	Minutes	0′	15′	30′
Sod. Pentobarb. 135 mg/Kg i.p.	Normal Saline Solution—Control	4/10	3	45	84	61	54
"	5-(1, 3 Dimethyl Butyl) 5-Ethyl Barbituric Acid (Sod. Salt) 15 mg/Kg i.p.	2/10	3	36	85	69	43
"	1-*n*-Butyl, 5-Ethyl, 5-Methyl Barbituric Acid (Sod. Salt) 350 mg/Kg i.p.	0/10	—	—	87	33	—
"	5-(3, 3 Dimethyl Allyl) 5-Ethyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	6/10	3	14	79	58	45
"	5-Butyl Barbituric Acid (Sod. Salt) 2 grams/Kg i.p.	2/10	6	—	78	63	52
"	5-Ethyl, 5-Benzyl Barbituric Acid (Sod. Salt) 35 mg/Kg i.p.	0/10	—	—	76	42	—
"	5, 5-Dibenzyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	1/10	5	31	68	54	60
Hexobarbital Sodium 325 mg/Kg i.p.	Normal Saline Solution—Control	6/10	3	3	87	60	46
"	5-(1, 3 Dimethyl Butyl) 5-Ethyl Barbituric Acid (Sod. Salt) 15 mg/Kg i.p.	0/10	—	—	85	57	21
"	1-*n*-Butyl, 5-Ethyl, 5-Methyl Barbituric Acid (Sod. Salt) 350 mg/Kg i.p.	0/10	—	—	74	45	24
"	5-(3, 3 Dimethyl Allyl) 5-Ethyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	5/10	3	13	74	58	43
"	5-Butyl Barbituric Acid (Sod. Salt) 2 grams/Kg i.p.	5/10	4	7	92	69	58
"	5-Ethyl, 5-Benzyl Barbituric Acid (Sod. Salt) 35 mg/Kg i.p.	9/10	4	44	85	68	66
"	5, 5-Dibenzyl Barbituric Acid (Sod. Salt) 200 mg/Kg i.p.	10/10	4	35	88	64	67

* of those which survived.
** of all of those which were living at the indicated time period.

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NOTE ON THE EFFECT OF A PURIFIED CHOLINESTERASE PREPARATION ON THE HYPNOTIC AND TOXIC EFFECT OF BARBITURATES *

By Charles A. Leonard ** and Joseph W. E. Harrisson **

IT HAS been long recognized that most barbiturates exert some cholinesterase inhibiting activity in vitro as well as in vivo. Recently, Greig and Mayberry (1) demonstrated that cholinesterase inhibitors increase the penetration rate of barbiturates into the brain cells as well as their hypnotic activity. As a purified true-cholinesterase preparation (2) has been made available, it seemed to be of interest to test its effect on the hypnotic and toxic effect of barbiturates.

Because of the limited supply of the cholinesterase preparation and the enormous doses which may be required by any cellular enzyme given externally to exert any effect, only a small number of animals could be used. Several hundred mice used in a series of studies on barbiturate poisoning served as a control group. Eight Webster male mice of 20 Gm. body weight received 50 units of cholinesterase intravenously. Immediately afterwards, four received an LD_{50} dose of pentobarbital (135 mg/Kg i. p.); four received a hypnotic dose of 100 mg/Kg sodium hexobarbital (Evipal Sodium) †, i. p. Death rate and sleeping time of these animals fell into the range of that of the control animals.

This observation is in line with that of Beck (3) who did not find an important anticholinergic effects of this preparation and demonstrated that it rapidly disappears from the blood and the tissues.

* Supported by a grant from Eli Lilly and Company.

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† We are greatly indebted to Winthrop-Stearns, Inc. for supplying us with the purified true-cholinesterase preparation and with Evipal Sodium.

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RECENT ADVANCES IN THE CONTROL OF MALARIA

IN spite of our many advances in the field of insecticides and antimalarial agents, malaria continues to be a serious problem in many countries. India, for example, is stated to have 100 million cases a year with 1 million deaths directly attributable to the disease and another million in which malaria is an indirect factor. In many other countries, malaria causes great disability among the population, lowering agricultural output and reducing the standard of living.

Mosquito Control

The control of malaria, to be effective, must be pressed on many fronts. In some areas, certain steps are quite effective while, in others, they must be supplanted or supplemented by other measures. As an example, one might cite the drainage of swamps and marshlands which serve as breeding grounds for the insect vectors, the anopheles mosquitoes. This is not practical in many places where the terrain is predominantly marshy and wet.

The spraying of such areas with oils to destroy the larval stage of anopheles mosquitoes was, until recently, the chief method of malaria control. It was by this means that the control of malaria in Cyprus was attained.

With the discovery of the remarkable insecticidal action of D. D. T., residual spraying techniques were developed against adult mosquitoes. This has proven the most effective measure of all in mosquito control insofar as reduction in the incidence of malaria is concerned. The technique of residual spraying consists of spraying either a solution or a suspension of D. D. T. on the domestic resting places (walls and ceilings) of mosquitoes. Many formulas have been recommended. A 5 per cent solution of D. D. T. in kerosene has been used, a 5 per cent suspension of D. D. T. using a "wettable" powder, and a 5 per cent emulsion made by diluting an oil concentrate with water. All possible domestic resting places are sprayed including barns, churches, factories, outhouses, etc. Often, it is found desirable to combine larval control by pond and marsh spraying with residual domestic spraying for best results.

The success of mosquito control will be seen from the following data collected in Greece. Here, there were 2 million cases of malaria in 1942. In 1949, only 40,000 cases were recorded. This means a saving of man workdays equivalent to the addition of 200,000 workers per year. In one area alone, an increase in crop production of over 20 per cent resulted. In Mauritius, through the cooperation of its government, mosquito control has reduced the reported cases from 1050 monthly in 1948 to none in 1951. Here, it is believed that malaria will soon be totally eradicated from the island whereupon spraying control measures may be discontinued.

Antimalarials

Concurrent with the progress and program in mosquito control, there have been tremendous strides made in the chemotherapy of malaria. Quinine, which once was thought the ideal antimalarial, is now considered practically obsolete except as an adjunct to certain synthetic drugs, such as pentaquine. Even the synthetic, quinacrine (Atabrine), is no longer considered a good antimalarial since others are available which have been proven far superior.

Before considering the modern, efficient, antimalarial agents, it might be wise to review briefly the transmission of malaria, the cycle between man and mosquito, and the asexual and sexual phases of the parasite. An understanding of these is essential if one is to understand the treatment of malaria and the selection of the proper drug to accomplish a given purpose.

Malaria, as a disease, must alternate between man and the mosquito in order for it to spread from one person to another. It is for this reason that the elimination of mosquitoes breaks the chain of transmission. Man is not the only animal that can harbor the parasite and, thus, there exists a continuing animal reservoir which cannot be eliminated.

There are many different species of the anopheles mosquito; some are much more implicated as malaria vectors than others. The malaria parasite belongs to the genus, *Plasmodia*. Morphologically, four distinct species are recognized: *Plasmodium ovale* is rare and of little clinical importance. *P. malariae* and *P. vivax* have much in common and, for therapeutic purposes, they are considered together. *P. falciparum* is a species quite unlike the others and must be considered separately. Each species is known to have many different strains and these may differ greatly in their response to therapy.

The malaria parasite passes through its sexual cycle in the mosquito and, the asexual cycle in man. In order to perpetuate its existence, it must alternate between these two hosts. When an infected mosquito feeds on a human being, the malaria parasites, at the stage of development known as sporozoites, enter the blood stream. Very shortly thereafter, these sporozoites leave the blood stream and enter the tissues of the host. About a week later, blood forms called trophozoites appear and these invade the red cells and undergo nuclear subdivision. Finally, the red cell is ruptured and a number of spore-like bodies called merozoites are released which again invade other red cells and the process is repeated. A regular pattern of red cell destruction with the release of toxins is established and this coincides with the regular chills and fever so characteristic of malaria. Sexual forms of the parasite also appear in the blood at regular intervals. These are called gametocytes. It is these which are conveyed to the stomach of a biting mosquito in which the sexual cycle then takes place. It is interesting to note that persons who have acquired considerable immunity to malaria by prolonged exposure do not harbor sexual parasites in their blood. Non-immunes who contract malaria are the ones responsible for the infection of mosquitoes and the rapid spread of the disease.

The treatment given malaria is closely tied up with many factors, including the species of the invading parasite. *P. falciparum* is believed to be the most recently acquired malaria infection in man. By contrast, if untreated, it is the most dangerous but, when treated, the easiest cured. The reason for this is simple. This type of malaria does not produce persistent fixed tissue forms. Once the parasite enters the blood phase, the tissue forms become inactive. If, then, a drug is given to clear the blood stream of parasites, no relapse takes place when therapy is stopped.

In *P. vivax* and *P. malariae* infections, the fixed tissue forms persist and release parasites to the blood stream at intervals. For this reason, even if blood forms are destroyed, a relapse is very likely unless suppressive therapy is continued or some drug is used which will destroy the fixed tissue forms of the parasite. While this type of malaria does not have as high a mortality rate as *P. falciparum,* it causes untold difficulty by reason of relapses. It is interesting to note here that, in temperate zones, the latent period before a relapse with *P. vivax* may be several months while, in the tropics, the strains of

P. vivax cause relapses in just a few weeks if suppressive therapy is discontinued.

In *P. vivax* or *P. malariae* infections, two courses of action are available: to continue suppressive therapy indefinitely or to attempt a radical cure to destroy the fixed tissue forms. If the patient lives in a region where malaria is prevalent, it seems foolish to attempt a radical cure since reinfection *via* infected anopheline vectors is likely. If he leaves the region and goes to a place where malaria reinfection is unlikely, a regimen to produce a radical cure is advisable.

Considering the life-cycle of the malaria parasite, two other approaches to malaria can be seen. A drug which destroys the invading sporozoites from the mosquito before they enter the tissues of the host or destroys the tissue stages before blood forms are released would be a causal prophylactic. A drug destroying the sexual form in man's blood (gametocyticidal) would prevent its spread by preventing the infection of mosquitoes. Drugs having some efficiency in these directions are known. In order to simplify our discussion of the antimalarial drugs themselves, they shall be divided into four groups:

(a) Suppressives.
(b) Drugs for radical cure.
(c) Causal prophylactics.
(d) Gametocyticidal agents.

Suppressives

Quinine—This drug, historically, was the first effective antimalarial agent known to man and a wealth of literature concerning it has been published. Quinine, today, is not considered highly as an antimalarial. To relieve an attack, a dose of 2 Gm. per day (as sulfate) for 7 days is recommended. In falciparum malaria, it is not too effective. As a suppressive, a dose of 0.65 Gm, per day is given. Side reactions (cinchonism) are frequent and, sometimes, severe. In vivax malaria, a relapse may take place 1-2 weeks after cessation of therapy with tropical zone vivax.

Quinacrine—This drug, commonly known at Atabrine (Winthrop-Stearns) is far superior to quinine but it, too, has many disadvantages. To relieve an attack, the dose (as the hydrochloride) is 0.2 Gm., 3 times a day for 5-10 days. As a suppressive, the dose is 0.1 Gm. daily.

Quinacrine is actually a yellow acridine dye and it tends to stain the skin and nails. It also sometimes causes nausea and has been known to produce toxic psychoses. Relapse in vivax malaria after it is discontinued usually takes place in 4-6 weeks (tropical zone).

Chloroquine—This drug, also known as Aralen Diphosphate (Winthrop-Stearns), is an excellent suppressive. It is the diphosphate of 7-chloro-4-(4′-diethylamino-1′-methylbutylamino) quinoline. For the control of an attack of malaria, the dose is 1 Gm. (as the diphosphate) followed by 0.5 Gm. after 6-8 hours and, then, 0.5 Gm. on two consecutive days. This rapidly controls the attack. As a suppressive, the dose is 0.3 Gm. twice a week or 0.5 Gm. once a week.

Chloroquine is almost devoid of toxicity in the dosage given and it does not stain the skin as does quinacrine. It has the further advantage in vivax malaria, when therapy is stopped, of not being followed by a relapse in less than 7 weeks. This is a much longer period than with quinacrine.

Amodiaquine—This is also known under the proprietary name, Camoquin (Parke, Davis & Co.). It is a chloroquinoline, as is chloroquine. Its chemical name is 4-(3′-diethylaminomethyl-4′-hydroxyanilino)-7-chloroquinoline. Amodiaquine is given in a single dose of 0.6 Gm. in the treatment of malaria. It is quite similar to chloroquin in its relative effectiveness and it is difficult to point to a clear cut superiority of either. Some reports claim that amodiaquine controls fever more rapidly than chloroquine and that, with larger doses, relapses are few.

Amodiaquine is also an effective suppressive.

Chloroguanide—This drug is also known as Proguanil, Paludrine, and Guanatol. Chemically, it is unlike all other antimalarials. Its chemical name is N_1-p-chlorophenyl-N_5-isopropyl biguanide and it is used as the hydrochloride. This drug caused great excitement at the time of its introduction since, in addition to its action on the erythrocytic forms of the parasite, it seems to be a causal prophylactic against *P. falciparum* and to have gametocyticidal action.

The dose in an attack is 100 mg., three times a day for 10 days. In falciparum malaria, this dose may need to be doubled or, better yet, supplemented the first few days with 0.65 Gm. of quinine. When used alone in falciparum malaria, chloroguanide is too slow in controlling the parasitemia.

As a suppressive, chloroguanide is given in a dose of 100 mg. either daily or twice weekly. It is almost devoid of toxicity.

Experience has shown that chloroguanide is less rapid than chloroquin or amodiaquine and that there is some evidence that *P. falciparum* may acquire resistance to it. When given with pamaquine, it can be used for the radical cure of malaria but it is doubtful that this is the best therapeutic approach.

Pyrimethamine—This antimalarial was developed as a result of studies being conducted on folic acid antagonists. Proguanil (chloroguanide) was found to be similar in action to certain pyrimidines and these, in turn, were found to be more potent antimalarials than proguanil itself. It is now known that proguanil is converted into a diaminopyrimidine in the body. A large number of pyrimidine derivatives were synthesized and tested with the result that 2,4-diamino-5-(4′-chlorophenyl)-6-ethyl pyrimidine was selected as the most active. This substance was first referred to as B. W. 50-63 and it is now also known as Daraprim (Burroughs-Wellcome). It is 60 times as active as proguanil against *P. gallinaceum* in the chick and 200 times as active against *P. berghei* in the mouse. The drug acts against the parasites in the blood stream; particularly, the schizonts and, in a very small dose. The dose required is only 0.5 mg./Kg. body weight. It is nontoxic and tasteless. The suppressive dose is 25 mg. a week in one dose.

Further evidence concerning the relative merits of this drug as compared with either amodiaquine or chloroquine is needed. Cross resistance between pyrimethamine and proguanil has already been reported with *P. falciparum* and this is, of course, a drawback. Pyrimethamine has also been criticized for a rather slow effect in controlling an attack as is the case with proguanil. In the dose used as an antimalarial, its folic acid antagonism is not of significance.

Drugs for Radical Cure

There are, today, a number of drugs which will eliminate the fixed tissue forms of relapsing malaria (*P. vivax* and *P. malariae*). While the continued and prolonged use of suppressives such as chloroquine may exhaust the fixed tissue forms, other more potent drugs will do this in a very short time. Amodiaquine is claimed to result in both clinical and radical cure of most cases but these claims need verification that only further study can give.

Pamaquine—This drug, known also as Plasmochin (Winthrop-Stearns), is an 8-amino-quinoline derivative. Its chemical name is 6-methoxy-8-(1′-methyl-4′-diethylaminobutylamino) quinoline. When using pamaquine, it is best to administer it with quinine, chloroguanide, or chloroquine to control the parasitemia. Quinacrine should never be given with pamaquine since it increases its toxicity and causes hemolytic anemia. A number of regimens using pamaquine and quinine have been suggested. One is as follows: Give 0.33 Gm. of quinine sulfate plus 0.01 Gm. of pamaquine every 8 hours for 7 days—then, allow a 7 day rest period; re-institute therapy for 5 days—then, allow a 7 day rest period; again, institute therapy for 5 days. Another regimen directs the use of 0.65 Gm. of quinine sulfate and 0.01 Gm. of pamaquine every 8 hours for 10-14 days.

Pentaquine—This drug was developed during World War II for the radical cure of malaria. It, too, is an 8-aminoquinoline and its chemical name is 6-methoxy-8-(5′-isopropyl aminoamylamino) quinoline. Pentaquine is believed less toxic than pamaquine. It is given with quinine as is pamaquine. The regimen prescribed is 0.01 Gm. plus 0.33 Gm. of quinine sulfate every 4 hours for 14 days. This dosage level of pentaquine (0.06 Gm./day) produces some toxic reactions and patients should be kept under close observation for hemolytic anemia. Reducing the dosage level of pentaquine to 0.03 Gm./day greatly reduces the incidence of toxicity. As with all 8-aminoquinolines, including pamaquin, the drug is much more toxic in Negroes and other highly pigmented persons than it is in whites.

Isopentaquine—This drug is isomeric with pentaquine. Its chemical name is 8-(4′-isopropylamino-1′methylbutylamino) 6-methoxyquinoline. It is claimed to be less toxic than pentaquine. It is given at the same dosage level.

Primaquine—This also is an 8-aminoquinoline but it appears to be the drug of choice at present. Chemically, it is 6-methoxy-8-(4′-amino-1′-methylbutylamino) quinoline. The dosage regimen is 26.5 of the diphosphate (15 mg. base) for 14 days. For the first 3 days, chloroquine is administered concurrently as follows: the first day, 3 doses of 0.3 Gm. (base); then, 0.3 Gm. the second and third day. Doses of 30 mg. of primaquine per day are not recommended in highly pigmented persons since there is a danger of hemolytic anemia. The 15 mg. daily dose seems entirely safe and effective for all persons

except those suffering from concomitant diseases affecting the bone marrow or blood. As in the case of other 8-aminoquinoline, quinacrine therapy should not be given concurrently.

Causal Prophylactics

There is evidence that both chloroguamide and primaquine have an action against both the sporozoites and the tissue stages preceding clinical malaria in both *P. falciparum* and *P. vivax*.

Gametocyticidal Drugs

The gametocytes of *P. falciparum* tend to remain in the circulating blood even after the asexual forms are destroyed. The 8-aminoquinolines as a group are gametocyticidal in action and they tend to prevent transmission from man to mosquito. In the case of *P. vivax* the gametocytes do not persist after the asexual forms are destroyed in the circulating blood. Therefore, all suppressive drugs have an indirect gametocyticidal action.

In conclusion, the author wishes to point out that the means for the complete control of malaria are at hand. The only need is to extend these means to those who need them and to train pharmacists, physicians, and other health workers in their use.

THE STORY OF IODINE *

By Louis Gershenfeld **

IODINE was discovered by Bernard Courtois, a Frenchman, about 140 years ago.

The discovery of iodine may be looked upon as a result of war-fostered research. At the time, France was engaged in the Napoleonic wars and she was isolated from foreign sources due to a blockade by the British Navy and the allied armies, and therefore could not obtain the necessary amount of nitrate required for the production of gunpowder. To supply her requirements of this strategic material, nitre beds were established from which the nitrate was produced.

Courtois was one of those engaged in this industry. In his operation he used crude soda ash, which he obtained from the ashes of seaweed. The seaweed, unknown to him, also contained iodine compounds so that when heated, it yielded a violet colored vapor. Some time later, a sample came into the possession of J. L. Gay-Lussac, distinguished French chemist, who studied its properties, recognized it as a new element, and named it "iode," from the Greek word meaning violet colored.

Iodine is an elemental substance; that is to say, it is one of the ninety-eight known elements—chemically indestructible entities. Iodine, as in the case of all elements, cannot be broken down by chemical means into simpler components. It is a solid, crystalline substance, grayish black in color, and has a bright metallic lustre resembling somewhat the glint of lead or steel filings. The brown "iodine tincture" familiar in the home medicine cupboard is merely a small quantity of the solid dissolved in diluted alcohol.

Excepting the possible occurrence of elemental iodine vapor in the air near certain iodine-rich mineral springs, iodine never occurs free in nature. It always is found combined with other elements, either in the form of more or less simple inorganic salts or in the form of rather complex organic compounds. Although not found in large quantities, iodine in the form of its compounds is distributed almost

* Delivered over WFIL-TV—"University of the Air"—Friday, April 24, 1953.

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everywhere. It is present in many land waters and in the sea. Many plants contain it; and, it is found in higher animals as one of the essential elements of life.

However, the substances which characteristically contain iodine compounds in relatively large quantities are seaweeds, sponges and corals; the underground waters from certain deep oil-wells, borings and mineral springs in California, Java, Russia and Italy, and, most impressive of all, the vast natural deposits of caliche, the crude nitrate-bearing earth found in the northern part of Chile. Even in these, however, the proportion of iodine is very small.

There are large numbers of iodine-containing compounds and preparations marketed which are very useful and of considerable interest. These include preparations containing free (elemental) iodine, those yielding or liberating free (elemental) iodine, the inorganic iodides and the iodine-containing organic compounds. Many of them have played and are playing important roles in the laboratory and in research, in the development of new processes, new products and better methods of testing. Others find important industrial application in the production of various dyes and many high purity chemical compounds, in photography, in metallurgy, in electricity and in electronics. Witness such diversified uses as employing silver iodide as a smoke for the seeding of clouds to induce rainfall, and using sodium iodate to improve the bread-making qualities of certain kinds of flour.

Of interest in medicine is the use of atomic energy in diagnosis, therapy and research. Of particular significance is the radiation from Radioactive Iodine (I^{131}), used as a tracer and for the treatment of selective cases of thyroid disease. The layman, of course, is more familiar with the use of iodine products and preparations in the fields of medicine and public health. But even for medicinal use, numerous iodine compounds with unrelated actions are employed in many different specialized uses. They have been employed as antiseptics, fungicides, protozoacides and insecticides, as drugs administered in different combinations in the prevention and treatment of certain disease conditions, as clinical laboratory reagents, as aids in x-ray diagnostic procedures, in nutrition, in sanitizing procedures and as therapeutic agents in various thyroid conditions and in many other abnormalities.

Let us briefly review some of these uses in medicine and public health. The adult human body contains about 25 milligrams (approximately 3/8 grain) of iodine, present in combination with other

elements, of which about 15 milligrams (approximately ¼ grain) are in the thyroid gland. The minimum daily iodine requirement is 0.1 milligram, or 36.5 milligrams (approximately 3/5 grain) per year. An adequate intake of iodine is especially needed for the production of thyroxine, the thyroid hormone which is responsible for normal thyroid function. Thyroxine participates in the regulation of the circulatory, muscular, nervous and reproductive systems and of other endocrine glands and in carbohydrate metabolism, growth, nutrition and proper water balance. If iodine is deficient and thus there is a decrease in thyroxine secretion, the gland undergoes hypertrophy (abnormal increase in size), a condition known as simple goiter. This is easily recognized among humans and lower animals by the marked swelling which develops in the region of the neck. Goiter is especially prevalent in certain parts of the United States (Great Lake regions) and other areas of the world (as the Alpine countries of Europe).

In these so-called Goiter Belts, the vegetables grown in the existent iodine-poor soil are very low in iodine content, as is also the drinking water, with the result that goiter is prevalent. Administration of minute quantities of iodides for the prevention of goiter is inexpensive yet the most effective of all prophylactic procedures. The Council on Food and Nutrition of the American Medical Association has approved Iodized Salt for general use in foods as the most satisfactory means of supplying the nutritional need for iodine. Iodized table salt contains one part of potassium iodide in each 10,000 parts of salt, a concentration which results in the ingestion of approximately 3 milligrams or 1/20 grain of potassium iodide (equivalent to approximately 2.3 milligrams or 3/80 grain iodine) for every ounce of Iodized Salt.

Used internally, definite results are obtained with various iodine compounds in the rapid absorption of certain inflammatory exudates and gummy tumors; these so-called gummata (gumma-singular) diminish or disappear under adequate treatment.

Time does not permit to consider the iodine preparations used in veterinary medicine. However in passing, may I direct your attention to the feeding of farm animals with iodinated proteins to obtain increased and prolonged milk yields and in the feeding of hens to increase egg production. This is in addition to their use among lower animals just as iodine products are used by humans.

X-rays are frequently used for diagnostic purposes in conjunction with substances, so-called radiopaque media or x-ray contrast media,

which have the ability to absorb them (the rays) strongly. Many iodine combinations have proved useful for this purpose by rendering opaque to the x-ray the various parts of the body to be examined, thus making diagnosis by x-ray an easier task.

Finally, last but most important, you are all familiar with the wide use of free iodine and its preparations as antiseptics, employed in various combinations in the prevention and treatment of infections and also with its use in sanitization procedures.

Solutions containing free iodine have been employed throughout the World as antiseptics for nearly a century. Scientists everywhere during this entire period have revealed that solutions containing free iodine possess in the highest degree the prerequisites of the ideal effective antiseptic for many and varied uses. Iodine Solution containing 2% free iodine in distilled water, in which a soluble iodide is present to keep the iodine in solution, and Iodine Tincture, containing 2% free iodine in diluted alcohol (final alcohol content, 47%), are the iodine preparations of choice used most frequently today in this country as antiseptics for the skin, in wounds, on cuts and abrasions and for the treatment of various skin infections. When they are employed on the human body as skin antiseptics to prevent or treat infections, these solutions containing free iodine have the following properties: (1) high bactericidal and fungicidal activity, (2) low tissue toxicity, (3) freedom from specificity, i.e., attack all kinds of microorganisms, (4) rapid action, (5) penetration, (6) effectiveness in the presence of organic matter, especially blood, pus, oil, grease and soap, (7) safety margin on dilution, (8) effectiveness when exposed to different temperatures (especially low), (9) stability, (10) ease of application, (11) ready availability, (12) low cost, (13) no objectionable odor, and (14) color, to delineate area treated.

For the disinfection of clinical thermometers, immersion for 5 minutes in solutions containing 2% free iodine, preferably preceded by an effective cleaning procedure will be found to be suitable.

You may have heard of tablets of tetraglycine hydroperiodide, which liberate free iodine, for canteen use in the disinfection of water by our military. One tablet, or its equivalent of six minims of the 2% free iodine preparations, per quart of water for 10 to 20 minutes will assure you a safe potable water for human consumption. Weaker concentrations of iodine are being effectively employed in swimming pools for water sanitization.

Eating and drinking utensils especially if they are used by the sick can be sanitized by immersion in a solution containing free iodine, prepared by adding a teaspoonful of the 2% free iodine preparation (solution or tincture) to a pint of water.

I am at the end of my story due to the limited time available. What have we learned? One impression stands out conspicuously. Iodine has been serving Mankind for over a century; and each generation adds to the old but still modern uses and finds ever increasing new applications, as iodine continues its usefulness in serving all of us.

SELECTED ABSTRACTS

Effect of Broad Spectrum Antibiotics on Tumor Inducing Viruses. J. L. Ambrus, C. M. Ambrus, C. N. Sideri, J. W. E. Harrisson. *Antibiotics and Chemotherapy, 3,* 16-22 (1953).

The authors investigated the effect of aureomycin, terramycin, chloramphenicol and PA 96 (a new antibiotic from Chas. Pfizer and Co.) upon myxoma virus (OA strain), fibroma virus (Moses strain), Lucke's leopard frog kidney adenocarcinoma and Bittner's milk factor virus (from C_3H mice).

Eleven day old embryonated white leghorn eggs were inoculated in the chorioallantois with dilutions of myxoma virus ranging from 10^{-1} to 10^{-5}. This was followed immediately by the antibiotics at a dosage level of 0.1 mg./egg for aureomycin, and 0.2 mg./egg for the other antibiotics. Membranes were harvested after 72 hours of incubation at 37° C. and lesions recorded.

Groups of New Zealand white female rabbits received subcutaneously ten LD doses of myxoma virus. Aureomycin 50 mg./Kg., and chloramphenicol 50 mg./Kg., both twice daily subcutaneously, and terramycin 50 mg./Kg., twice daily orally, were administered to the respective test groups until death.

Additional groups of rabbits were treated with the respective antibiotics as in the myxoma studies, each rabbit also received a cutaneous inoculation of 0.2 ml. of a dilution series ranging from 10^{-1} to 10^{-8} from a fibroma-infected testicle suspension. The diameter and height of each tumor was estimated daily and tumor volume calculated.

Four hundred Rana pipiens collected in the area of Vermont were injected in the ventral lymph sac with 0.5 ml. of 10 per cent suspension of pooled kidney adenocarcinoma in frog Ringer solution. Test groups received 10 mg./Kg. of aureomycin, terramycin, and chloramphenicol daily by gastric intubation for two weeks. Then a concentration of 5 mg./liter of the respective antibiotic was maintained in the holding baths for two months. After seven months all survivors were sacrificed and autopsied noting the presence or absence of kidney adenocarcinoma.

Fifty female C_3H mice which had received the milk factor from their mothers were fed from weaning through the experimental period with powdered Rockland complete rat diet containing 240 mg./Kg. of aureomycin. Fifty mice were maintained as a control. Milk factor extract was prepared aseptically by pooling lactating mammary glands, spleens, lungs, kidney and blood of 10 C_3H mice from each group, homogenizing in a refrigerated Waring blendor and filtering through gauze. Aliquots were incubated aseptically for two hours at room temperature with 10 mg./ml., of aureomycin, terramycin and chloramphenicol. Groups of ten female C_3Ht Jax mice two to three weeks old were injected intraperitoneally with 0.1 ml. of the respective homogenates. Ten mice received no milk factor. The mice were kept in breeding units of one male to five females. Offspring of the third litter of each generation were inbred and observed further.

The authors report that they observed no significant difference between control and antibiotic test groups in their experiments.

Antibiotics in the Treatment of Acute Bacillary Dysentery. Garfinkel, B. T., Martin, G. M., Watt, J., Payne, F. J., Mason, R. P., and Hardy, A. V. *J. A. M. A. 151*:1157 (1953). Sulfonamide resistant cases of shigellosis among war prisoners in Korea were treated with oxytetracycline (terramycin), aureomycin, chloramphenicol and Polymyxin B. This therapy was compared with general supportive therapy (I. V. fluids and electrolytes, rest, sedatives) and sulfonamide therapy. A total of 1,408 patients were treated. All were hospitalized with severe dysentery and all had positive bacteriological cultures. No unique types of organisms were isolated. The Flexner group predominated, the Shiga bacillus occurred in less than 1 in 200 cases, and *Shigella sonne* (which is usually more resistant to sulfonamides) occurred in less than 3 per cent.

After 7 days of treatment 29 per cent of the cases treated by the supportive method were still culturally positive, 25 per cent of those treated with sulfadiazine, 12 per cent of those treated with Polymyxin B, 1 per cent of those treated with chloramphenicol or aureomycin, and none of those treated with terramycin was still culturally positive. Four regimens were used with aureomycin, chloramphenicol, and terramycin in an attempt to determine the size of dose required.

The regimens employed were 10 Gm. in 4 days, 4 Gm. in 7 days, 4 Gm. in 24 hours, and 2 Gm. in a single dose. After 7 days there was no statistically significant difference in the results obtained with these four regimens. With terramycin all were negative but with aureomycin and chloramphenicol 3 and 5 per cent, respectively, were positive after the 7 days. Therefore, the authors concluded that the best regimen was 4 Gm. in 3 doses within 24 hours.

Excretion of Phenolsulfonphthalein as an Aid to the Diagnosis of Hypertension. Vallance-Owen, J. *The Lancet 1*:721 (1953). Following cardiac infarction or for any other reason in which blood pressure has fallen, particularly in older patients, it is difficult to diagnose hypertension. It had been observed that the phenolsulfonphthalein (P. S. P.) excretion in two hours was frequently decreased below normal in hypertensive patients, although other kidney function tests were usually normal. Therefore, the author conducted a study on four groups of patients: (1) a group of 31 controls all essentially normal and with no hypertension; (2) a group of 25 patients with hypertension without heart failure; (3) a group of 21 patients with hypertension with heart failure; and (4) a group of 16 patients with heart failure but without hypertension.

An intramuscular injection of 6 mg. of P. S. P. was given and urine samples were voided at one-hour and two-hour intervals. Separate P. S. P. determinations were made on these samples. In the controls a mean of 68 per cent had been excreted by those under 40 years of age and 62 per cent by those over 45 years of age. In group 2 the mean value was 41.5 per cent with only 2 patients showing more than 50 per cent. All but 2 of the patients in group 2 were over 45 years of age. In group 3 the P. S. P. excretion was less than 45 per cent in all but one with a mean value of 34.3 per cent. All but one of the patients were over 40 years of age. In group 3 the P. S. P. excretion was over 45 per cent in all but one patient with the mean value being 54 per cent. All but one of the patients were over 45 years of age.

From these results it would seem to appear that the excretion of P. S. P. over a period of two hours can be of definite assistance in diagnosing hypertension, whether or not heart failure is present.

Although the excretion is decreased in heart-failure alone, there is a significant further reduction if hypertension is or has been present. An excretion of less than 50 per cent in the absence of heart failure or 45 per cent if heart failure is present strongly supports the diagnosis of hypertension.

The Effects of Estrogen-Androgen Mixtures in the Climacterium. Shearman, A. M., Vogel, M., and McGavack, T. H. *Geriatrics 8*:155 (1953). A comparison of the effect of an estrogen-androgen mixture in relieving the symptoms of the climacterium in women as compared with the use of estrogen and androgen alone was made by the authors in a study on 29 women in the menopause.

The estrogen-androgen mixture was given as a tablet containing 0.25 mg. of diethylstilbestrol and 5.0 mg. of methyltestosterone. The estrogen and the androgen were given as the same substance in the same dose, but singly. In 30 trials a single tablet was given daily. In 35 additional trials doses of 2 to 5 tablets daily were employed. Additional improvement was obtained in 15 of the 16 patients in whom the larger dosage was necessary. Control periods of an average of 4.8 weeks were interspersed between trial periods.

There were daily vaginal smears taken as an objective criterion of results. However, the patient's symptoms, subjectively, and not the vaginal smears were used as a criterion for determining the duration of administration of a potent preparation, the degree of increase in the daily dose, and the time for reinstitution of a control period and use of the placebo.

Improvement in subjective symptoms was 83 per cent in the trials in which the combined therapy was given as compared with 75 per cent in the trials in which the estrogen was given and 61 per cent in those in which the androgen was given. Of those reporting improvement 14 per cent, 29 per cent, and 11 per cent, respectively, reported complete remission of symptoms. The authors stated that there was a statistically significant difference between those reporting improvement during the use of the estrogen-androgen mixture as compared with those receiving the androgen alone. Altering the vaginal smears were observed in those receiving both the mixture and the estrogen alone.

Cross Resistance to Antibiotics. Fusillo, M. H., Romansky, M. J., and Kuhns, D. M. *Antibiotics & Chemotherapy 3*:35 (1953). Six strains each of *Staphylococcus aureus, Streptococcus fecalis, Escherichia coli,* and *Aerobacter aerogenes* were grown in the presence of increasing concentrations of aureomycin, terramycin, and chloramphenicol through 10 transfers. These organisms were then tested for their sensitivity to each of these antibiotics as well as to penicillin and streptomycin. All strains were tested for their sensitivity to each of the antibiotics at the beginning of the experiment.

The results of this *in vitro* study indicated that upon exposure to aureomycin or terramycin given strains of bacteria tend to develop resistance simultaneously to both of these antibiotics. Cross resistance between chloramphenicol and aureomycin or terramycin occurred most frequently and markedly with *A. aerogenes,* less so with *E. coli,* and rarely with the gram-positive organisms. Cross resistance occurred in five of the six strains of *A. aerogenes* to aureomycin, chloramphenicol and terramycin. However, following exposure to aureomycin the increase was small with respect to chloramphenicol. The strains of *E. coli* failed to demonstrate cross resistance to aureomycin and terramycin when resistance to chloramphenicol was induced.

Exposure of the gram-positive bacteria to the wide spectrum antibiotics failed to produce increased or decreased sensitivity of these organisms to penicillin. Exposure to the wide spectrum antibiotics also failed to produce any significant change in sensitivity of *S. fecalis, E. coli,* or *A. aerogenes* to streptomycin.

Toxicity of Penicillin and Aureomycin in Guinea Pigs. Ambrus, C. M., Sideri, C. N., Johnson, G. C., and Harrisson, J. W. E. *Antibiotics and Chemotherapy, 2*:521 (1952).

A study was undertaken to investigate the possible allergic reaction of Guinea pigs to pencillin and aureomycin and protection afforded by antihistaminics.

English smooth-hair guinea pigs used in the experiment were divided into 4 groups. Group 1 received: 10,000 units/Kg penicillin subcutaneously; group 2: 10,000 units/Kg penicillin accompanied by pretreatment for 15 minutes by a subcutaneous injection of 10 mg/Kg N-dimethylamine propyl-phenothiazine hydrochloride (Phenergan);

group 3: 10,000 units/Kg *l*-ephenamine penicillin G (Compenamine) intramuscularly; and group 4:10 mg/Kg Phenergan alone. The animals treated only with Phenergan all survived while those treated with penicillin and Phenergan had an 80% mortality. All animals treated with compenamine or penicillin died, however those guinea pigs injected with the former lived on the average 6.3 days while those treated wtih crystalline sodium penicillin G lived on the average of 3.2 days.

Three groups of guinea pigs were treated as follows: Group 1: 10 mg/Kg aureomycin subcutaneously, group 2: 10 mg/Kg aureomycin and given 15 minutes beforehand 10 mg/Kg Phenergan subcutaneously, group 3: 10 mg/Kg Phenergan alone. Treatment for six weeks resulted in no deaths in group 3 treated only with Phenergan while 70% died in the Phenergan-aureomycin treated group. Only 30% died when given aureomycin only. Median death time was 9 days for animals treated with Phenergan-aureomycin and over 6 weeks for those given only aureomycin.

Presence of penicillin producing fungi in the lungs of sacrificed animals was established, the antibiotic activity of colonies of the isolated fungi was tested against *Staphylcoccus aureus* directly and after incubation with penicillinase. Isolated intestines, uteri and lung preparations were prepared in order to detect the possible presence of sessile antibodies, no such antibodies were found. Pathologic, anatomic and histologic examination produced no significant results.

From these studies the authors concluded that (a) Penicillin is more toxic to guinea pigs which are known to be susceptible to allergic conditions as compared with most other species of experimental animals; (b) an antihistaminic drug provided definite protection against the toxic effect of penicillin; (c) a hypoallergenic penicillin (compenamine) was less toxic to guinea pigs than crystalline sodium penicillin; (d) since guinea pigs die within the first few days of penicillin administration, it is not likely that sensitization has taken place durng the experimental period; (e) since penicillin producing fungi were found in lungs, previous sensitization is a possibility; (f) no sessile antibodies could be demonstrated against penicillin in guinea pig organs; (g) aureomycin has a lower chronic toxicity than penicillin in guinea pigs.

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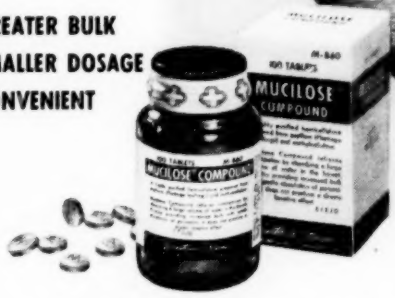

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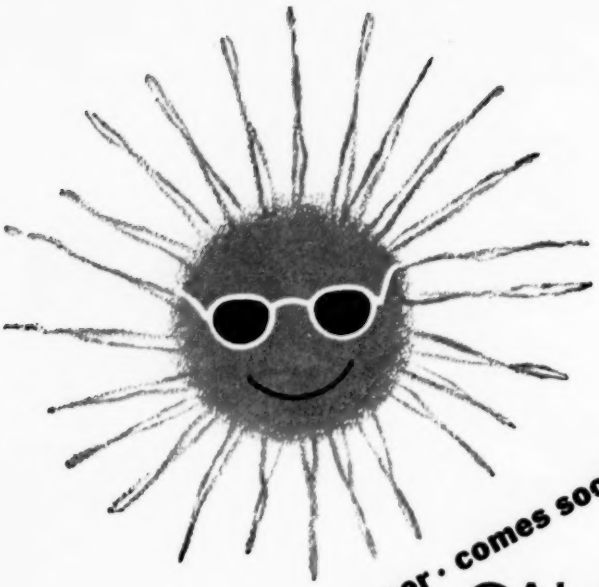

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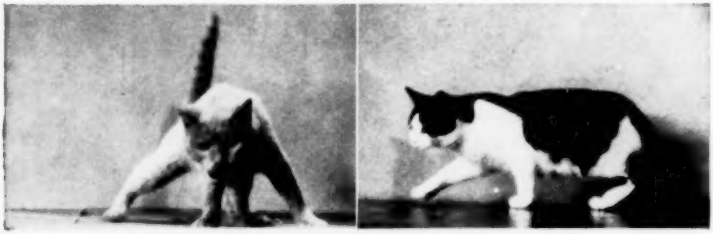

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